Sub 4 cont

C5 concld.

applying hydrated precursor paste to a surface of the prosthesis, the hydrated precursor comprising an amorphous calcium phosphate and a promoter, whereby the hydrated precursor is converted at the implant site to a hardened calcium phosphate product wherein the hardening process is associated with an endothermic reaction [poorly crystalline apatitic calcium phosphate] and the [poorly crystalline apatitic] hardened calcium phosphate is resorbed and replaced thereby with bone.

REMARKS

Claims 1-7, 9-16 and 21-26 are pending in the above-identified application and stand rejected under 35 U.S.C. §112, first and second paragraphs, and §103(a). Claims 2 and 25 have been amended with this response. Reexamination and reconsideration of the claims as currently pending are respectfully requested.

I. Applicants' Invention.

The present invention is directed to methods of treating a bone defect and/or of embedding a prosthesis at a bone site. In one aspect of the invention a poorly crystalline apatitic calcium phosphate is employed in the method having the unique and desirable properties of strong bioresorbability and bone ingrowth at the implant site. Strong bioresorbability is defined as a resorption rate characterized in that, when placed in a rat intramuscular site, at least 1 g of the PCA calcium phosphate is at least 80% resorbed within one year.

In another aspect of the invention, a hydrated precursor is introduced to a bone site for the purposes of treating a bone defect or embedding a prosthesis. The hydrated precursor comprises an amorphous calcium phosphate and a promoter and is converted *in vivo* at the implant site to a hardened calcium phosphate. The hardening process is associated with an endothermic reaction, whereby bone is formed at the implant site. The endothermic reaction provides significant advantages over the prior art processes because living tissue has a very low tolerance to heat and heat-induced necrosis of neighboring tissue is avoided.

II. Amendment of the claims.

The specification has been amended to include a passage describing the endothermic reaction associated with the hardening of the hydrated precursor. Support for the amendment is found in co-pending application U.S.S.N. 08/729,344, which has been incorporated in its entirety into the instant application. See, page 1, lines 11-12, of the instant application.

Claims 2 and 25 have been amended to recite a hydrated precursor paste that hardens in a process associated with an endothermic reaction. Support for this amendment is found in the newly added text to the specification at page 5, line 6.

II. Rejection of the claims under 35 U.S.C. §103(a) as being unpatentable over Rey *et al.*, Symposium Abstract (1993) ["Rey"], Eanes *et al.*, *Calc. Tiss. Res.* **5**:133 (1970) ["Eanes I"] or Eanes *et al.*, *Nature* **208**(5008):365 (1965) ["Eanes II"], optionally in view of USP 4,429,961 to Niwa *et al.* ["Niwa"].

Claims 1-7, 9-16 and 21-26 stand rejected. The Examiner asserts that the primary references establish that a poorly crystalline apatitic (PCA) calcium phosphate was known in the prior art. Further, the Examiner states that the claimed compositions do not exhibit improved working properties and thus are equivalent to the prior art examples. See, Paper No. 16, pages 2-3. Applicants respectfully traverse the rejection.

(A) With respect to claims 1 and 26 and those dependent thereon.

Claims 1 is directed to a method of treating a bone defect including introducing a strongly resorbing, poorly crystalline apatitic calcium phosphate to the bone defect site, whereby the material is resorbed and bone is formed at the site. Claim 26 is directed to a prosthetic device including a strongly resorbing, poorly crystalline apatitic calcium phosphate in surface contact with prosthesis locatable at a bone site. Applicants do not dispute that the prior art has prepared apatitic calcium phosphate compositions of low crystallinity. Applicants submit, however, that there has been no teaching or suggestion of a low crystallinity apatitic calcium phosphate possessing the claimed bioresorbability and bone ingrowth properties that make it especially desirable and useful in the treatment of bone defects. The prior art calcium phosphate materials have been prepared using

methods distinguishable from that of the instant invention, further supporting Applicants' position that the product possesses unique and non-obvious properties.

Rey states that bioresorbable calcium phosphates may be used as a support for bioactive molecules which can be progressively released as the calcium phosphate is resorbed. Rey then goes on to describe a poorly crystalline apatite having high specific surface area. Rey does not state and provides no proof that, in fact, the calcium phosphate apatites reported therein are resorbable. Rey provides no information about its material that would suggest its ability to promote bone ingrowth and therefore there is no teaching of using the material in sites where bone ingrowth is desirable. Lastly there is no teaching or suggestion of using this material for treating a bone defect. In sum, there is no teaching or suggestion of a calcium phosphate material having rapid bioresorbability, coupled with bone ingrowth at an implant site.

Eanes I is a scholarly reference that investigates the chemically definable local structure of amorphous calcium phosphate. The reference describes the crystalline and amorphous reaction products resulting from heating of amorphous calcium phosphate at very high temperatures. Eanes I reports the formation of "non-crystalline" and crystalline phases. Nowhere is a poorly crystalline apatitic calcium phosphate observed or reported. There is no suggestion that any of the many phases, compositions and structures described therein is a PCA calcium phosphate, let alone that such a material could have utility in the treatment of bone defects. The reference simply fails to teach the claimed

material and its use as recited in the instant invention.

Eanes II reports on the compositional and structural changes that occur in a suspended solid in the preparation of synthetic calcium phosphates. The reference reports that amorphous calcium phosphate was converted into a poorly crystalline hydroxyapatite. As with Eanes I, this is a scholarly report on the chemical reactivities of calcium phosphate in solution. It does not suggest the use of a compound in a method for treating a bone defect, as is recited in the instant claims. The properties of a PCA calcium phosphate relevant to treating bone defects, e.g., bioresorbability and bone ingrowth into the implant, are not disclosed and there can be no motivation to use the disclosed materials in the claimed manner.

Niwa is relied upon as disclosing Ca/P ratios also included in the instant specification. Niwa's contribution to the art is the use of a sintered hydroxyapatite having microporosity which permits the growth of cells in the interstitial spaces. There is no teaching or suggestion of a poorly crystalline apatitic calcium phosphate. The Examiner has noted the small grain size of the hydroxyapatite crystal reported by Niwa (50 Å-10 μm) and considers the material to be poorly crystalline. However, "poorly crystalline", as used in the present invention, refers to the quality of the crystals and not the size of the crystal. The powders of Niwa are prepared by sintering starting materials at temperatures in the range of 500-1100 °C --temperatures known to produce crystalline product. Even powders of very small size will exhibit sharp peaks in an x-ray diffraction

pattern if the powders are crystalline and thus they lack a feature indicative of poorly crystalline hydroxyapatite, namely, a broad, featureless x-ray diffraction pattern. See, Response filed November 13, 1997, pages 5-7.

There is no suggestion in Niwa that the hydroxyapatite implant is resorbable and indeed, Applicants have previously argued that Niwa does not teach a resorbable hydroxyapatite implant. See, the Response filed July 16, 1998, at page 8; and the Response filed November 13, 1997, at page 11. The asserted crystalline nature of the Niwa powder is consistent with the observation that they are not resorbed in a bone setting.

In summary, the Examiner has provided a variety of references, two of which do not even disclose a PCA calcium phosphate, one of which observes conversion of PCA calcium phosphate from amorphous calcium phosphate in solution, and one of which describes a PCA calcium apatite for use in releasing a biomolecule. There is no teaching or suggestion in any of these references to use a highly bioresorbable PCA calcium phosphate at a bone defect site, with the subsequent replacement of the material by bone.

The Examiner is suggesting that references which disclose the existence of a poorly crystalline apatitic calcium phosphate render the claimed invention obvious, despite the fact that none of the cited references (except Niwa) give any indication that the material may be introduced to a bone site. None of the materials are shown to be capable of bone ingrowth and/or bioresorbability. In the case of Niwa, the calcium

phosphate is clearly not bioresorbable and not conducive to bone ingrowth replacing the implant material. The existence of a poorly crystalline apatitic calcium phosphate does not render obvious its use in the treatment of bone defects, absent a showing that those materials possess some properties making them desirable for such a use.

(B) With respect to claims 2 and 25 and those dependent thereon.

Claims 2 and 25 are directed to a method of treating a bone defect or embedding a prosthesis by applying a hydrated precursor paste to a bone site (or a prosthesis in claim 25) and effecting *in vivo* conversion of the hydrated precursor paste into a hardened product in an endothermic process. None of the references teach a hardenable amorphous calcium phosphate paste, leave alone a paste that hardens in an endothermic reaction.

<u>Eanes I</u> describes amorphous calcium phosphate, but does not describe a paste comprised of amorphous calcium phosphate or a paste which forms a hardened product in an endothermic process.

<u>Eanes II</u> describes conversion of an amorphous calcium phosphate into a PCA calcium phosphate, but does not disclose a precursor paste which converts into a hardened product in a process associated with an endothermic reaction.

<u>Rey</u> teaches hardening of a gel or slurry in a process which includes slow dehydration and shrinkage. Such a process is neither possible nor desirable *in vivo*. Rey does not disclose the use of a hardenable amorphous calcium phosphate paste, much less its introduction into a bone site. Nor would one be motivated to introduce the Rey

material into a bone site because the hardening process described by Rey is inoperatable *in vivo* sites. Rey neither expressly nor inherently teaches a paste which hardens in association with an endothermic reaction.

Niwa adds water to its crystalline hydroxyapatite powder to obtain a hydroxyapatite paste for filling defects in a bone. Niwa does not disclose the use of amorphous calcium phosphate in the preparation of a hydrated precursor paste. Niwa does not report hardening of the material, much less a hardening reaction in an endothermic process.

In conclusion, none of the references, alone or in combination, comes close to teaching or suggesting the claimed invention, which includes providing an amorphous calcium phosphate paste, introducing the paste into a bone site, and hardening the paste in an endothermic process to treat a bone defect. The references simply fail to identify the use of an amorphous calcium phosphate-containing paste in the treatment of bone defects. Further, they fail to teach or suggest use of a hardening reaction that progresses endothermally.

The Examiner has suggested that the prior art calcium phosphate materials must possess the claimed properties because the instant specification discloses methods of making the claimed inventive material that are the same as in the prior art. Applicants respectfully disagree. The calcium phosphate materials of Rey are prepared by slow drying of a gel of unknown composition. Eanes I ignites amorphous calcium phosphates

at high temperatures. Eanes II reports the formation over a period of days or hours of a PCA calcium phosphate from a solution containing amorphous calcium phosphate in a mother liquor. Niwa heats non-amorphous precursor materials at high temperatures (500-1300°C). All of these procedures are distinguishable from the instant invention, in which an amorphous calcium phosphate and a promoter react at body temperature to form a hardened calcium phosphate in a process associated with an endothermic reaction.

For the foregoing reasons, it is submitted that none of the cited references, Rey, Eanes I, Eanes II and Niwa, either alone or in combination, suggest the claimed invention. It is respectfully requested that the rejection be withdrawn.

III. Rejection of the claims under 35 U.S.C. §103(a) as being unpatentable over USP 5,037,639 to Tung *et al.* ["Tung"], USP 5,053,212 to Constantz *et al.* ["Constantz '212"] or USP 5,542,973 to Chow *et al.* ["Chow '973"], optionally in view of Glimcher et al., *Phil. Trans. R. Soc. Lond. B* **304**:479 (1984) ["Glimcher"].

Claims 1-7, 9-16 and 21-26 stand rejected. The Examiner suggests that the methods of making a poorly crystalline hydroxyapatite are described in the primary references. The Examiner points out that Glimcher discloses a poorly crystalline hydroxyapatite structure. See, Paper No. 16, pages 3-4. Applicants respectfully traverse the rejection.

(A) With respect to claim 1 and 26 and those dependent thereon.

Applicants do not dispute that Glimcher discloses an apatitic calcium phosphate

composition of low crystallinity. Applicants submit, however, that there has been no teaching or suggestion in either the primary or secondary references of a low crystallinity apatitic calcium phosphate possessing the claimed bioresorbability and bone ingrowth properties that make it especially desirable and useful in the treatment of bone defects and the embedding of a prosthesis at a bone site.

Tung discloses the use of amorphous calcium phosphate in remineralizing teeth. The remineralized apatitic calcium phosphate is intended to become a permanent part of the tooth. There is no teaching of a *resorbable, poorly crystalline* calcium phosphate, nor is there any teaching of bone ingrowth at an implant site. Indeed, such features recited in the instant claims are contrary to the intended use of the Tung material as a permanent replacement for a tooth lost to tooth decay.

Chow '973 teaches a calcium phosphate prepared by the reaction of tetracalcium phosphate and a second, sparingly soluble calcium phosphate. Constantz '212 discloses an acid/base reaction between a calcium source and a phosphoric acid source to obtain hydroxyapatite or other calcium phosphate minerals.

Neither of the references discloses a poorly crystalline hydroxyapatite, much less one having the stated resorbability. Chow '973 discloses a calcium phosphate product having a Ca/P ratio very close to that of crystalline hydroxyapatite, that is, 1.67. For example, Example 7 describes a powder in which the Ca/P = 1.64. Such starting compositions favor the formation of crystalline products. Constantz '212 describes

formation of various crystalline forms of calcium phosphate, depending upon the starting Ca/P ratio.

The fact that the prior art has identified and characterized a poorly crystalline hydroxyapatite, e.g., in Glimcher and Eanes II, supports Applicants position that the calcium phosphates of Chow '973 and Constantz '212 are not poorly crystalline hydroxyapatites. Inventors Chow and Constantz, as active researchers in this field, would certainly have been aware of the work of Glimcher and Eanes II. Had the material of Chow '973 or Constantz '212 been a poorly crystalline hydroxyapatite, Chow and Constantz would have recognized it for what it was and identified it accordingly.

Furthermore, there is no teaching or suggestion of a strongly resorbable calcium phosphate, defined as having a resorption rate characterized in that, when placed in a rat intramuscular site, at least 1 g of the PCA calcium phosphate is at least 80% resorbed within one year. Chow '973 describes the material as capable of undergoing "gradual biointegration" and being "gradually replaced over the course of weeks and months, at least in part" (col. 5, lines 63-67).

Applicants previously have provided documentation supporting their position that Chow does not produce a strongly resorbable calcium phosphate. See, Response filed July 16, 1998. Chow and Takagi (inventors of Chow '973) have co-authored several papers reporting on the resorbability of their apatitic calcium phosphate. Applicants again draw the Examiner's attention to the two references submitted in the Response filed

July 16, 1998. Exhibit I ("Long Term Follow-Up of Hydroxyapatite Cement (HAC) Implants for Craniofacial Reconstruction") reports "excellent" bone substitution in craniofacial reconstruction and states that the "amount of HAC resorption/bone replacement was greater than 80% at 30 months". Thus, a Chow cement is only 80% resorbed after 2 ½ years, which falls outside the resorbability profile of the claimed materials. Likewise, Exhibit II ("Facial Skeletal Augmentation Using Hydroxyapatite Cement") reports that after nine months "the proportion of hydroxyapatite implant replaced by bone and osteoid was 42% and 45%" for two dogs that underwent hydroxyapatite cement implantation at the supraorbital ridges of the cranium using cement prepared from tetracalcium phosphate and anhydrous dicalcium phosphate, as reported in Chow '973.

Glimcher is a scholarly reference that investigates the validity of the Amorphous Calcium Phosphate theory of bone development. Glimcher discloses an x-ray diffraction pattern of an *in vitro* prepared sample of poorly crystalline hydroxyapatite, but provides no further characterization of the material and indeed, there is no indication that the material exhibits bone ingrowth or bioresorbability. As was true for Eanes I and II, above, such studies do not disclose the use of a compound in a method for treating a bone defect, as is recited in the instant claims. The properties of a PCA calcium phosphate relevant to treating bone defects, e.g., bioresorbability and bone ingrowth into the implant, are not disclosed and there can be no motivation to use the disclosed materials in

the claimed manner.

In summary, the primary references Tung, Chow '973 and Constantz '212 teach introduction of a calcium phosphate to a bone site, which is neither a PCA calcium phosphate nor a strongly resorbing calcium phosphate. None of the references teach or suggest a calcium phosphate material capable of bone ingrowth. Glimcher describes an *in vitro*-prepared poorly crystalline hydroxyapatite, but does not describe any of its properties. In particular, the reference is entirely lacking in characterization of those properties relevant to treatment of bone defects, namely, bioresorbability and bone ingrowth at the implant site. There is no teaching or suggestion of using a poorly crystalline calcium phosphate demonstrating strong bioresorbability and bone ingrowth in either the primary or secondary references.

Claim 26 includes the further feature that a prosthesis is located at the implant site and the paste is in surface contact with the prosthesis. None of the references even mentions a prosthesis, leave alone its use in combination with the inventive hardenable paste.

The Examiner has suggested that the methods taught by Chow '973 or Constantz '212 can be used to obtain the claimed PCA calcium phosphate. Applicants respectfully disagree. The instant specification describes a method of making a PCA calcium phosphate that uses amorphous starting materials, e.g., amorphous calcium phosphate. A promoter is used to aid in the conversion of the amorphous calcium phosphate into an

apatitic calcium phosphate, such that no long range order (crystallinity) is introduced into the material during conversion. Further, the specification discloses that the conversion and hardening process associated with the formation of the inventive PCA calcium phosphate are endothermic processes.

Constantz '212, in contrast, uses standard crystalline materials and relies on acid/base chemistry to drive the reaction to form the desired calcium phosphate in crystalline form. Such processes are inherently exothermic.

Likewise, Chow '973 admits that the formation of the hardened calcium phosphate is not an endothermic reaction, characterizing the reaction as "isothermic" in that negligible heat is generated (col. 5, lines 37-40). Applicants provide further evidence of the exothermic nature of the Chow process in a copy of a letter found as Attachment 1. The letter is addressed to Dr. Lawrence Chow who acknowledges his agreement with the contents of the letter. The letter characterizes Chow's work as "calcium-phosphate cements for use in medical applications...that are exothermic in nature". The '973 patent is listed as one of the technologies encompassed by this discussion.

Tung describes the gradual dissolution of amorphous calcium phosphate and redeposition of crystalline calcium phosphate. The method is not relevant to the formation of a PCA calcium phosphate.

Thus, the methods provided in the prior art references are distinguishable from those used to prepare the claimed PCA calcium phosphate and Applicants assert that they

do not teach, inherently or otherwise, the formation of the claimed inventive PCA calcium phosphate.

(B) With respect to claims 2 and 25 and those dependent thereon.

Tung teaches that an amorphous calcium phosphate is remineralized to form crystalline apatitic calcium phosphate. There is no teaching of preparing a paste comprising amorphous calcium phosphate and a promoter (which may be another calcium phosphate or other nucleating agent). Nor is there any teaching of the paste forming a hardened calcium phosphate that hardens in an endothermic process or of bone ingrowth at an implant site.

Chow '973 describes a single example in which an amorphous calcium phosphate is reacted with tetracalcium phosphate. Chow '973 provides no evidence to suggest that the reaction product hardens in an endothermic process. Nor is there any teaching or suggestion of introducing the hydrated precursor into a bone site, where it is hardened *in vivo* into a hardened calcium phosphate in association with an endothermic reaction. As stated herein above, Chow's process is an isothermic process, generating a negligible, but positive, amount of heat (Chow col. 5, line 33-42). Inventor Chow himself characterizes the process as being "exothermic in nature". See, Attachment 1.

Constantz '212 discloses an acid/base reaction between a calcium source and a phosphoric acid source to obtain hydroxyapatite. There is no teaching or suggestion of introducing a paste comprised of an amorphous calcium phosphate and a promoter into a

bone site and hardening the paste *in vivo*. Certainly the starting acid and base components are too caustic or corrosive to be introduced into a body site until the reaction has progressed to near neutrality. Significantly, there is no teaching of an endothermic hardening process. Acid-base reactions, such as those relied upon in the hardening reactions of Constantz, are typically exothermic.

Glimcher is a scholarly reference that investigates the validity of the Amorphous Calcium Phosphate theory of bone development. There is no teaching or suggestion of an amorphous calcium phosphate paste, indeed the only possible mention of amorphous calcium phosphate was as a minor, naturally-occurring component in bone. As was true for Eanes I and II, above, such studies do not disclose the use of a compound in a method for treating a bone defect, as is recited in the instant claims. There is no teaching of forming a hardenable paste comprising amorphous calcium phosphate. Nor is there any teaching of an endothermic hardening process.

In conclusion, none of the references, alone or in combination, comes close to teaching or suggesting the claimed invention, which includes providing an amorphous calcium phosphate paste, introducing the paste into a bone cite and hardening the paste *in vivo* in an endothermic process. Certainly none of the references suggest its introduction in surface contact with a prosthesis at a bone site, as recited in claim 25. The cited art makes reference to isolated features of the claimed method, but fails to provide the requisite teaching or suggestion that would lead one skilled in the art to combine the

references in a manner to produce the claimed invention. Such suggestion must be found in the prior art and not in the Applicants' specification.

For the foregoing reasons, it is submitted that none of the cited references, Tung, Chow '973, Constantz '212 and Glimcher, either alone or in combination suggest the claimed invention. It is respectfully requested that the rejection be withdrawn.

IV. Rejection of the claims under 35 U.S.C. §112, first and second paragraphs.

Claims 1-7, 9-16 and 21-26 stand rejected under 35 U.S.C. §112, first and second paragraphs. The Examiner states that the claims recite a "poorly crystalline" material, which in not descriptive of an improved poorly crystalline material. Applicants respectfully traverse the rejection.

Firstly, Applicants note that the Examiner has not elaborated as to what requirements of statute the claims have failed to meet. Applicants address all requirements set forth in §112, first and second paragraphs, for the purpose of providing as full a response as possible. If the Examiner feels additional comments is required, further explanation is requested.

It is submitted that use of the term "poorly crystalline" is distinct and definite as required by the statute. Applicants have already fully addressed this issue in a prior response. See, Amendment and Response filed November 13, 1997. Applicants are not suggesting that this term have any meaning other than that generally accepted and understood in the art.

Further, Applicants submit that they have fully and adequately described the material used in the method of the invention by requiring that the material have the following advantageous properties: (1) a poorly crystalline apatitic microstructure; (2) strong bioresorbability, characterized in that, when placed in a rat intramuscular site, at least 1 g of the PCA calcium phosphate is at least 80% resorbed within one year, and bone is formed at the implant site; and (3) the ability to promote bone in-growth at the implant site. Applicants submit that such description definitely and distinctly claims the material to be used in the claimed method of the invention and further submit that the claims satisfies the requirements of §112, second paragraph.

Applicants also submit that the specification contains a written description of the claimed invention and sets forth the best mode contemplated by the inventors for carrying out their invention, as required by §112, first paragraph. Further, the specification sets forth the manner and method of making and using the claimed invention. For example, the specification explains the desirability of using amorphous starting materials to retain the long-range disorder in the calcium phosphate product. The specification further describes the conversion of amorphous calcium phosphate into a poorly crystalline hydroxyapatite and enumerates the factors relevant to the selection of appropriate promoters and amorphous calcium phosphates. See, pages 16-22 and Examples 1-6, and 8. Methods of introduction of the material to a bone site are clearly described. See, pages 22-24. Methods for assessing bioresorbability of the material are set forth. See,

Examples 16 and 17. Biointegration of new bone at the implant site is clearly established. See, Examples 16, 19, 20-23, and 25. It is submitted that the specification fully enables the practice of the claimed invention, as is required by §112, first paragraph.

Withdrawal of the rejection is respectfully requested.

V. Submission of related embodiments

The Examiner has requested identification of the closest working embodiments in the prior art to the poorly crystalline apatitic calcium phosphate of the invention. The request was made earlier of the Applicants and they have responded in the Response of July 16, 1998 by submission of Exhibits 1 through 7.

VI. Additional comments.

Applicant notes that the Examiner's Action was mailed to the incorrect address. Effective immediately, please address all communication in this application to:

Mary Rose Scozzafava, Ph.D.
Clark & Elbing LLP
176 Federal Street
Boston, MA 02110

Enclosed is a petition to extend the period for replying for two months, to and including March 8, 1999.

If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: March 5, 1999

Mary Rose Scozzafava

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ATTACHMENT 1

Laurence C. Chow, Ph.D., Chief Research Scientist
Paffenbarger Research Center
National Institute of Standards and Technology
Gaithersburg, MD 20899
Fax: 301-963-9143

September 17, 1996

Dear Larry,

It was very enjoyable meeting with you during your visit to Boston last week.

To follow up on our discussion, it is believed that ETEX Corporation and your laboratory may benefit mutually from scientific collaboration on certain calcium phosphate research. The purpose of this letter is to provide a delineation between this contemplated collaborative research and the previous and on-going calcium phosphate research which you have conducted. Hopefully, clarity at this stage will help to avoid potential misunderstandings in the future.

It is our understanding from our discussion with you that the technology in your existing patents and on-going research relates to calcium-phosphate cements for use in medical applications is based on reactions that are exothermic in nature. ETEX's approach, in contrast, does not necessarily rely on exothermic reactions and ETEX does not wish to pursue with you any collaborative research into the development of calcium phosphate cements for use in medical applications based on exothermic reactions. More specifically, ETEX has done no work and makes no claims that would infringe α-TCP patent 5,525,148 or tetracalcium phosphate-based patents RERE33,161; RE33,221, 5,522,893, 5,552,973; 5,545,254.

It is my understanding that we both felt that these differences offer significant delineation between our technologies, so that we may move forward with discussions regarding future collaborations.

It is my further understanding from our discussion with you that your ability to work with ETEX on a new calcium phosphate system, is free from conflicts, obligations or commitments with our third party interests.

Sincerely,

D. Duke Lee, PhD.

Agreed:

Lawrence C Chow

Lawrence Chow, Ph.D.

9/20/96

Date

TOTAL P.01

TOTAL P.01